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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
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EXAMINER

RABIN, E.
ART UNIT PAPER NUMBER

1644

DATE MAILED: 02 12/96

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

- ☒ Responsive to communication(s) filed on 11/28/97
- ☒ This action is FINAL.
- ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

- ☒ Claim(s) 10-14 and 25-28 is/are pending in the application.
Of the above, claim(s) _____ is/are withdrawn from consideration.
- ☐ Claim(s) _____ is/are allowed.
- ☒ Claim(s) 10-14 and 25-28 is/are rejected.
- ☐ Claim(s) _____ is/are objected to.
- ☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

- ☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
- ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
- ☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
- ☐ The specification is objected to by the Examiner.
- ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

- ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).
- ☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been
- ☐ received.
- ☐ received in Application No. (Series Code/Serial Number) _____
- ☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

- ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

- ☒ Notice of Reference Cited, PTO-892
- ☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 9
- ☐ Interview Summary, PTO-413
- ☐ Notice of Draftsperson's Patent Drawing Review, PTO-948
- ☐ Notice of Informal Patent Application, PTO-152

—SEE OFFICE ACTION ON THE FOLLOWING PAGES—

DETAILED ACTION

Response to Amendment

1. Effective February 7, 1998, the location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1644, Technology Center 1600.
2. Applicant's amendment was received November 28, 1997 as Paper No. 8.
3. This application is a continuation-in-part of application Serial Number 08/405,496. .
4. Applicant's election without traverse of Group II, Claims 10-14 in Paper No. 8 is acknowledged.
5. Claims 25-28 have been added. Claims 1-9 and 15-24 have been canceled. Claims 10-14 and 25-28 are pending and currently under examination.
6. The text of those sections of title 35 USC not included in this Action can be found in the prior office action (Paper No. 5).

Claim Rejections - 35 USC § 112

7. Claims 10-14 and 25-28 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly

connected, to make and use the invention, for the same reasons as set forth in Paper No. 5.

8. Applicant's arguments filed November 28, 1997 as Paper No. 8 have been fully considered, but they are not persuasive.

9. Applicant argues that a *prima facie* case of non-enablement has not been established. Applicant argues that the biological activity of a protein as a vaccine does not require knowledge of its structure. Applicant further argues that art-accepted neutralization assays can be used to successfully determine the biological activity of portions of *Clostridium botulinum* type A, B, and E toxin. However, Applicant's claims read on portions as small as one amino acid. The specification indicates that "fragments may range in size from four amino acid residues to the entire amino acid sequence minus one amino acid." There is insufficient teaching and guidance in the specification to indicate to one of skill in the art which "portions", when portions as small as four amino acid residues are considered, if administered, would result in the production of the neutralizing antibodies and thus the protection recited in the claims. The specification fails to provide sufficient guidance to enable one of ordinary skill in the art to make and use the claimed protein in a manner reasonably correlated with the broad scope of the claims including any number of fragments or portions of any size. *In re Fisher*, 1666 USPQ 19 24 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Here, the experimentation left to those skilled in the art is unnecessarily, and improperly extensive and undue. In addition, the specification does not enable the myriad of fusion proteins encompassed by the claims in view of the use of "comprising" language and with the reciting of "one or more" in the amended claims. One of skill in the art could not practicably generate neutralizing antibodies offering the protection recited in the claims without undue experimentation.

In view of the lack of predictability of the art to which the invention pertains and the limited working examples, the state of the prior art, the lack of guidance in the specification and the breadth of the claims, it would take undue experimentation to practice the invention as broadly claimed.

10. Claims 10-14 and 25-28 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, for the same reasons as set forth in Paper No. 5.

Applicant argues that "it is not the function of the claims to identify the relevant portions of the toxins, so long as identification of such portions is understood by the artisan from the specification's teachings." However, as the artisan would not necessarily know which portions would result in neutralizing antibodies, so the portions would not be understood by the artisan.

Applicant further argues that "at least a portion of" is not indefinite because through the use of common sense one would know that such language means "a fragment which includes both (a) fragments which constitute a 'portion' as described above, and (b) fragments which are larger in size than a 'portion'". In other words, the term 'at least a portion of' a toxin means fragments which range in size from 4 amino acids to the entire amino acid sequence of the toxin." However, because the claim uses "comprising" language and recites "at least a portion of one or more *Clostridium botulinum* toxins," the artisan does not definitely know what the final immunogen consists of. It is suggested that the specific portions of the *Clostridium botulinum* toxins be explicitly recited within the claim or this language be removed completely in order to obviate this rejection.

Claim Rejections - 35 USC § 103

13. Claims 10-14 and 25-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Thompson *et al.* [Eur. J. Biochem. 189: 73-81 (Apr 1990)] in view of Binz *et al.* [J. Biol. Chem. 265: 9153-9158 (June 1990)], Roitt [Essential Immunology, Sixth Edition, Blackwell Scientific Publications, Boston, MA, pp. 173-178 (1988)], LeClerc *et al.* [J. Immunol. 144 (8): 3174-3182 (Apr 1990)], Kleid [Annals NY Acad. Sci. 413: 23-30 (1983)], and Siegel [J. Clin. Microbiol. 26: 2351-2356 (Nov 1988)], for the same reasons as set forth in Paper No. 5.

Applicant argues that the Examiner has failed to meet the requirements of a *prima facie* case of obviousness. In response to applicant's arguments against the references individually, one cannot show non-obviousness by attacking references individually where the rejections are based on combinations of references. *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicant argues that the combined references do not teach all the elements of the claimed invention. Specifically, Applicant states that "independent Claim 10 does not require type A toxin because the language of Claim 10 expressly refers to only toxin types B and E, but not type A" and that any reference to *Clostridium botulinum* type A toxin is "irrelevant to a discussion of obviousness of independent Claim 10 and of Claims 11-14 which depend therefrom." Applicant repeatedly points out that references to type A toxin are irrelevant; see, for example, Paper No. 8: Page 11, Last Paragraph; Page 12, Paragraph 1; and Page 13, Lines 12-13. However, Claims 10 recites, "a vaccine comprising ..." and thus would encompass type A toxin, for example.

Applicant argues that art teaching methods of making vaccines using fusion proteins as immunogens is not relevant to the obviousness of the compound being claimed. (Page 12, Paper No. 8). However, the methods of the references have resulted in vaccines that make the compound of the claims obvious. Roitt, LeClerc *et al.*, and Kleid all teach fusion proteins comprising toxin proteins. Further the Examiner is permitted to rely on that knowledge that would be possessed by a person of ordinary skill in the art. See MPEP, "Applicant is reminded that once distinctions are identified between the claimed invention and the prior art, those distinctions must be assessed and resolved in light of the knowledge possessed by a person of ordinary skill in the art. Against this backdrop, one must determine whether the invention would have been obvious at the time the invention was made". Thus, knowledge available to of ordinary skill in the art would encompass the teachings of Roitt, LeClerc *et al.*, and Kleid as well as the textbook, Botulinum and Tetanus Neurotoxins [B. R. DasGupta, Ed., Plenum Press, New York (1993)] wherein La Penotiere *et al.* teach fusion proteins of *Clostridium botulinum* toxin and maltose binding protein. Vaccines taught in such references render the vaccine of the claims obvious.

Applicant argues that there would be no motivation to substitute the formalin-inactivated toxin with the claimed invention's fusion protein. In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, there is knowledge generally available to one of ordinary skill in the art. It is well known that recombinant fusion proteins offer the advantage of large scale production, the possibilities of altering "native" protein to

incorporate desirable characteristics (for vaccines, an example would be addition of highly immunogenic epitopes), and advantages for purification (the addition of "tags" to facilitate purification has been well known in the art). In addition to the evidence given earlier, Nygren *et al.* [Trends in Biotechnology 12 (5): 184-188 (May 1994)] teach the advantages of recombinant fusion proteins within their general review on bioprocessing (Page 188, in particular).

Applicant argues that the combined references do not teach a reasonable expectation of success in practicing the claimed invention. However, certainly the fusion proteins discussed as therapeutic agents in Roitt, LeClerc *et al.*, Kleid, La Penotiere *et al.* and Nygren *et al.* are all examples of successful vaccines.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

14. Claims 13 and 14 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Thompson *et al.* [Eur. J. Biochem. 189: 73-81 (Apr 1990)], Binz *et al.* [J. Biol. Chem. 265: 9153-9158 (June 1990)], Roitt [Essential Immunology, Sixth Edition, Blackwell Scientific Publications, Boston, MA, pp. 173-178 (1988)], LeClerc *et al.* [J. Immunol. 144 (8): 3174-3182 (Apr 1990)], Kleid [Annals NY Acad. Sci. 413: 23-30 (1983)], and Siegel [J. Clin. Microbiol. 26: 2351-2356 (Nov 1988)], as applied to claims 10-12 above, and further in view of Ford *et al.* [Protein Expression and Purification 2: 95-107 (1991)], for the same reasons as set forth in Paper No. 5.

Applicant argues that Ford *et al.* teaches use of fusion proteins for the recovery and purification of proteins, not for the generation of antibodies. However, in a 103 rejection, it is permissible to cite a reference that uses the product for a different reason

than the claimed invention. See MPEP 2144, "the reason or motivation to modify the reference may often suggest what the inventor has done, but for a different purpose or to solve a different problem. It is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by applicant. In re Linter , 458 F.2d 1013, 173 USPQ 560 (CCPA 1972) (discussed below); In re Dillon , 919 F.2d 688, 16 USPQ2d 1897 (Fed. Cir. 1990), cert. denied , 500 U.S. 904 (1991) (discussed below). Although Ex parte Levengood , 28 USPQ2d 1300, 1302 (Bd. Pat. App. & Inter. 1993) states that obviousness cannot be established by combining references "without also providing evidence of the motivating force which would impel one skilled in the art to do what the patent applicant has done " (emphasis added), reading the quotation in context it is clear that while there must be motivation to make the claimed invention , there is no requirement that the prior art provide the same reason as the applicant to make the claimed invention."

Applicant further argues that there is no expectation of success in being able to make vaccines which contain fusion proteins comprising a poly-histidine tract or making endotoxin-free vaccines. However, as stated above, the references themselves teach the success of such endeavors. With regards to fusion proteins comprising poly histidine, see again Nygren *et al.* [Trends in Biotechnology 12 (5): 184-188 (May 1994)].

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.


10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP


§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Evelyn Rabin, Ph.D. whose telephone number is (703) 305-6811. The examiner can normally be reached on Monday through Thursday from 7:30 AM to 6:00 PM.

12. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan, can be reached on (703) 308-3973. The FAX number for this Technology Center is (703) 305-3014 or (703)308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Technology Center receptionist whose telephone number is (703) 308-0196.


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February 17, 1998


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